Clinical impact of breast cancer genes

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Chapter 3

BRCA mutations in women with **ductal carcinoma *in situ***

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Abstract

Purpose The strength of the association between ductal carcinoma *in situ* (DCIS) and *BRCA* mutations has not been defined.

Experimental Design Mutation frequency was compared in three groups: 1) a prevalent series of women with DCIS, 2) an incident series of women with DCIS and 3) a clinic-based series of women with DCIS referred for hereditary cancer risk assessment. In groups 1 and 2, limited to Ashkenazi Jewish (AJ) cases, mutation frequency was compared to that in age-matched AJ controls with invasive breast cancer (IBC).

Results In group 1, 3/62 (4.8%) women with DCIS and 15/130 (11.5%) controls with IBC had *BRCA* mutations. In group 2, 0/58 (0%) women with DCIS and 6/116 (5.2%) controls with IBC had *BRCA* mutations (combined odds ratios (OR) in groups 1 and 2: 3.64, 95% confidence interval (CI): 1.06-12.46, p=0.04). In group 3, deleterious mutations were identified in 10/79 (12.7%) probands with DCIS, similar to for the frequency in IBC probands. In group 3, mutations were associated with family history (FH) of ovarian cancer (OC) (OR 13.35, 95% CI: 2.48-71.94, p=0.003) or early onset breast cancer (OR 16.23, 95% CI: 1.68-157.01, p=0.02) but not with AJ ethnicity or age at diagnosis.

Conclusions *BRCA* mutations were less frequent in women with DCIS not selected for FH or age at diagnosis than in women with IBC. Nonetheless, mutations are found in a significant proportion of women with DCIS who presented for hereditary risk assessment.

Introduction

Carriers of *BRCA1* and *BRCA2* mutations are at increased risk for multiple malignancies, especially breast and ovarian cancer. Cumulative breast cancer risks by age 70 are estimated to be 65% for *BRCA1* and 45% for *BRCA2* mutation carriers. Only 5-10% of invasive breast cancer (IBC) cases result from an autosomal dominant predisposition, but the prevalence of *BRCA* mutations is higher in young women and in women from populations with founder mutations.[1] For example, 1 in 40 Ashkenazi Jewish (AJ) individuals carry a founder mutation in the *BRCA1* or *BRCA2* gene.[2] Among AJ women diagnosed with breast cancer before the age of 40, 13-43% carry *BRCA* mutations.[3-5]

The incidence of ductal carcinoma *in situ* (DCIS), which is usually asymptomatic, has risen dramatically over the past 20 years due to the widespread use of screening mammography. The association of *BRCA* mutations with IBC is well established, but some controversy exists regarding whether DCIS should be considered a component of the *BRCA*-associated Hereditary Breast-Ovarian Cancer Syndrome (HBOCS). An early epidemiologic study reviewing 36 families with *BRCA1* mutations found only four cases of DCIS.[6] Subsequent studies evaluating pathological specimens from women with sporadic and *BRCA* mutation-associated IBC found less DCIS associated with the invasive cancers in the *BRCA1* mutation carriers than the sporadic cases.[7-9] These studies have led to the suggestion that the pre-invasive phase may be shortened or even absent in hereditary breast cancers, particularly those associated with *BRCA1* mutations.[8]

The identification of DCIS in risk-reducing mastectomy specimens from women with *BRCA* mutations and in biopsies done in response to abnormal screening studies in *BRCA* mutation carriers have led investigators to reconsider DCIS as a component of the HBOCS.[10-16] Claus *et al.* identified *BRCA* mutations in 3.3% of women with DCIS in a large, population-based study.[17] This mutation prevalence is similar to that described in population-based ascertainments of women with IBC. Other studies have also suggested that DCIS may be a component of the syndrome, although less characteristic than invasive disease. In Frank *et al.*'s description of genetic test results in 10,000 consecutive individuals, *BRCA* mutations were found in 13% of women with DCIS prior to age 50. Mutations were twice as prevalent in young women with IBC.[18] Hwang *et al.* found no difference in the prevalence of DCIS (with or without IBC) in mutation carriers and high-risk non-carriers, although the number of women with DCIS only was small.[19]

To further characterize the association between DCIS and *BRCA* mutations, we

compared the frequency of *BRCA* mutations in non-overlapping prevalent, incident, and clinic-based cohorts of women with DCIS and IBC. This approach allowed a comparison of mutation rates in groups not selected for genetic testing on the basis of either early diagnosis or family history (FH), and those referred for genetic risk assessment on the basis of these same parameters.

Materials and Methods

BRCA mutation prevalence was determined in three groups of women. The first two groups were prevalent (group 1) and incident (group 2) hospital-based ascertainments of AJ women with DCIS. Group 3 was a clinic-based ascertainment of AJ and non-AJ women with DCIS who presented to a hereditary cancer risk assessment service. All ascertainment and de-identification procedures were approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) Institutional Review Board (IRB).

Cases for group 1 were 120 Jewish women with DCIS drawn from a sample of cancer patients receiving follow-up care at Memorial Sloan-Kettering Cancer Center (MSKCC) ascertained without regard to age at diagnosis or FH. DNA for genotyping was extracted from lymphocytes from residual material remaining after routine blood tests and annotated with cancer type, age at diagnosis and religion (self-reported). At MSKCC, over 90% of individuals reporting Jewish religious preference were of Eastern/Central European (Ashkenazi) descent, thus all self-identified Jewish subjects were considered to be AJ. Cases associated with invasion or microinvasion were excluded, leaving a total of 66 women with pure DCIS eligible for study. Each case was age-matched (within +/- 3 years) to two female Jewish controls with invasive breast cancer (IBC) from the same ascertainment. Pathology reports were reviewed. Two cases with DCIS on the initial biopsy were found to have invasive disease at definitive surgery, and were excluded, leaving 64 DCIS cases and 132 IBC controls. Samples were irreversibly de-identified and genotyped for the Ashkenazi founder mutations (*BRCA1**185delAG, *BRCA1**5382insC, *BRCA2**6174delT) as previously described.[20] Genotyping failed for four samples (two DCIS, two IBC), leaving 62 DCIS cases and 130 IBC controls. Cases and controls for group 2 were drawn from a prospective ascertainment of women undergoing surgery at MSKCC between May 2001 and December 2004 for a new diagnosis of breast cancer, ascertained without regard to age at diagnosis or FH. The study database was queried and 58 Jewish women enrolled with a diagnosis of pure DCIS were selected. No woman in group 2 was a member of group 1. Each of these DCIS cases was age-matched (within +/- 4

years) to two Jewish women from the same ascertainment whose surgeries yielded IBC. Pathology reports were again reviewed. Samples were irreversibly de-identified and genotyped for the AJ founder mutations as described.

Group 3 was a clinic-based ascertainment of women evaluated by the Clinical Genetics Service at MSKCC between January 1995 and December 2005. In this interval, 104 female probands (AJ and non-AJ) with DCIS and 2,002 individuals with IBC presented for hereditary cancer risk assessment and subsequently underwent genetic counseling and testing. All subjects were participants in IRB-approved follow-up studies of women at hereditary risk for cancer and consented to genetic testing after appropriate pre-test counseling. Women were excluded from consideration as a case if a pathology report confirming DCIS was unavailable or if the report indicated definite invasion or microinvasion. In addition, women with a history of IBC or ovarian cancer (OC) prior to their diagnosis of DCIS were excluded. A total of 79 probands with pure DCIS remained for analysis. Factors potentially associated with *BRCA* mutations were assessed, including age at diagnosis of DCIS, FH of breast cancer or OC in at least one first and/or second degree relative, and ethnicity (AJ versus non-AJ). FH of breast cancer was considered to be early onset if the affected family member was diagnosed at age ≤50. All women who self-identified Jewish maternal and/or paternal descent were considered to be AJ. Probands for whom ethnicity was unknown were grouped with non-AJ probands for the analysis. Founder mutation analysis seeking the three common AJ founder mutations was performed for AJ women. Full sequence analysis (usually with rearrangement panel testing) was offered to all AJ probands without founder mutations, and was performed in 31%. Except for one non-AJ woman who underwent limited testing, genetic testing for all non-AJ probands involved full sequence analysis. For the statistical analysis, probands with genetic variants of uncertain significance were grouped with probands without mutations.

The *t*-test was used to compare means and Fisher's Exact test was used to compare proportions. Odds ratios (OR) were calculated to assess the strength of the relationship between DCIS and *BRCA* mutations. Univariate and multivariate logistic regression analyses were performed to identify factors predictive of mutations in the DCIS patients. Variables significant in univariate analyses were included in the multivariate model. p-Values < 0.05 were considered significant. All statistical tests were two-sided. Statistics were performed using Intercooled Stata Version 8.2 (Stata Corp.).

Results

Nested case-control studies of unselected AJ women with DCIS

Results from groups 1 and 2 are displayed in Table 1. For group 1, mean age at diagnosis did not differ between the DCIS cases and IBC controls (DCIS 56.5; IBC 56.7, *p*=0.90, overall age range, 23-85). AJ founder mutations were identified in 3 DCIS cases (4.8%) and 15 IBC controls (11.5%, *p*=0.19). Mean age was younger among those with mutations than those without mutations (mutation 50.6; no mutation 57.2, *p*=0.02). Of the DCIS patients with mutations in group 1, two occurred in *BRCA2* and one occurred in *BRCA1*.

Mean age also did not differ between the DCIS cases and the IBC controls in group 2 (DCIS 60.1; IBC 59.8, *p*=0.91, overall age range, 39-88). No *BRCA* mutations were identified among the DCIS cases in group 2. AJ founder mutations were identified in 6 IBC controls (5.2%) in group 2 (*p*=0.18). Mean age was not significantly younger among those with mutations than those without mutations (mutation 53.2; no mutation 60.1, *p*=0.15).

The overall prevalence of founder mutations in the combined ascertainments of AJ women with DCIS not selected on the basis of FH or age at diagnosis (groups 1 and 2) was 3/120 (2.5%). Founder mutations were 3.64 times more likely to be identified in age-matched IBC controls than in DCIS cases (combined OR 3.64, 95% CI: 1.06-12.46, *p*=0.04).

Table 1 Frequency of Ashkenazi founder *BRCA* mutations in women with DCIS and IBC

Group	No. *BRCA* mutations in DCIS cases	No. *BRCA* mutations in IBC cases	*p**	OR† (95% CI)
Unselected Ascertainment				
Group 1: Prevalent cases	3/62 (4.8%)	15/130 (11.5%)	0.19	2.57 (0.71-9.21)
Group 2: Incident cases	0/58 (0%)	6/116 (5.2%)	0.18	∞
Groups 1 and 2 combined	3/120 (2.5%)	21/246 (8.5%)	0.04	3.64 (1.06-12.46)
Clinic-based Ascertainment				
Group 3 compared to all IBC	10/79 (12.7%)	282/2002 (14%)	0.87	1.11 (0.58-2.15)
Group 3 compared to IBC at age < 50		222/1281 (17%)	0.44	1.37 (0.70-2.65)

***** *p*-Value for Fisher's Exact test comparing proportions of ductal carcinoma *in situ* (DCIS) cases and invasive breast cancer (IBC) controls with *BRCA* mutations

† Odds for mutation in IBC controls compared to DCIS cases

Clinic-based ascertainment

The characteristics of the 79 DCIS probands in the clinical ascertainment are displayed in Table 2. Of note, 45.6% had a FH of early onset breast cancer and 17.8% had a FH of OC. The mean age of diagnosis of DCIS was 46.9 (range 24-75).

Table 2 Characteristics of probands with ductal carcinoma *in situ* (DCIS) presenting for hereditary cancer risk assessment (group 3)

Characteristic	Proportion (%)
Ashkenazi Jewish (AJ)	42/79 (53.2%)
Age ≤ 50 at diagnosis of DCIS	56/79 (70.9%)
Family history (FH) of breast cancer (first or second degree)	61/79 (77.2%)
FH of early onset breast cancer (first or second degree)	36/79 (45.6%)
FH of ovarian cancer (OC)	14/79 (17.7%)

Among the 79 probands, 10 were found to have deleterious *BRCA* mutations (12.7%) and 2 were found to have variants of uncertain significance (2.5%). Seven of the 10 deleterious mutations identified were in *BRCA1* while 3 were in *BRCA2*. Deleterious mutations were identified in 5 of 42 AJ probands (11.9%) and in 5 of 37 non-AJ probands (13.5%) (p=1.00). Deleterious mutations were identified in 7 of 56 probands ≤ 50 years old (12.5%) and in 3 of 23 probands >50 years old (13.0%) at diagnosis of DCIS (p=1.00). In comparison, deleterious mutations were identified in 282 (14%) of 2,002 women with IBC seen during this same period, including 222/1,281 (17%) of those with IBC before age 50 (Table 1).

Table 3 displays the proportions of probands with *BRCA* mutations based on FH, stratified by ethnicity and by proband age at diagnosis. The groups with highest mutation prevalence were those with a FH of OC and/or early onset breast cancer. Among probands with family histories of both OC and early onset breast cancer, mutations were identified in 75%. No mutations were identified in non-AJ probands who did not have a FH of breast cancer and/or OC. Only one proband without a FH of breast cancer or OC, an AJ woman diagnosed at age 40, was found to carry a mutation. A FH of later onset (>50 years) breast cancer without a history of either early-onset BC or OC was not associated with mutations.

Table 3 Proportion of probands with DCIS in the clinical ascertainment with *BRCA* mutations, based on FH and stratified by ethnicity and by age at diagnosis of DCIS

FH*	All probands with DCIS	AJ probands with DCIS†	Non-AJ probands with DCIS†	Probands age ≤ 50 at diagnosis of DCIS†	Probands age > 50 at diagnosis of DCIS†
No FH of breast cancer or ovarian cancer (OC)	1/17 (5.9%)	1/11 (9.1%)	0/6 (0%)	1/10 (10%)	0/7 (0%)
FH of breast cancer in women age > 50, no FH of OC	0/20 (0%)	0/10 (0%)	0/10 (0%)	0/15 (0%)	0/5 (0%)
FH of breast cancer in women age ≤ 50 (with or without FH of breast cancer in women > 50), no FH of OC	3/28 (10.7%)	1/14 (7.1%)	2/14 (14.3%)	3/23 (13%)	0/5 (0%)
FH of OC, with or without FH of breast cancer	6/14 (42.9%)	3/7 (42.9%)	3/7 (42.9%)	3/8 (37.5%)	3/6 (50%)

***** Family history (FH) in first and/or second degree relatives
† All probands are listed in two subgroups (Ashkenazi Jewish (AJ) or non AJ and age ≤ 50 or > 50)

Table 4 Univariate and multivariate logistic regression analysis to identify predictors of *BRCA* mutations in DCIS probands in the clinical ascertainment

Predictors of *BRCA* mutations	Unadjusted OR (95% CI, *p-value*)	Adjusted OR† (95% CI, *p-value*)
Ashkenazi Jewish	0.86 (0.23-3.26, 0.83)	Not included
FH***** of breast cancer	2.94 (0.35-24.94, 0.32)	Not included
FH***** of breast cancer in women age ≤ 50	14.00 (1.68-116.85, 0.02)	16.23 (1.68-157.01, 0.02)
Proband age ≤ 50 at DCIS diagnosis	0.95 (0.22-4.06, 0.95)	Not included
FH***** of ovarian cancer	11.44 (2.65-49.45, 0.001)	13.35 (2.48-71.94, 0.003)

***** Family history (FH) in in first and/or second degree relatives
† Only variables significant in univariate analysis were included in multivariate model

Univariate logistic regression analysis identified FH of OC and FH of early onset breast cancer as factors predictive of mutation status among the DCIS probands in the clinical ascertainment. Ethnicity and proband age at diagnosis were not predictors of mutation status (p=0.83 and 0.95, respectively). In multivariate analysis, a FH of OC was associated with a 13-fold increase in the likelihood of identifying a mutation (OR 13.35, 95% CI: 2.48-71.94, p=0.003) and a FH of early onset breast cancer was associated with a 16-fold increase in the likelihood of identifying a mutation (OR 16.23, 95% CI: 1.68-157.01, p=0.02) (Table 4).

Discussion

The present study suggests that a diagnosis of IBC is more suggestive of an underlying *BRCA* mutation than a diagnosis of DCIS. In the nested case-control studies of AJ women with DCIS not selected for FH or age at diagnosis, mutations were identified in 2.5%, significantly lower than the frequency of mutations in age-matched controls with invasive cancer. Indeed, the prevalence of mutations in AJ women with DCIS was similar to the 1.8% (62/3434) observed by Hartge *et al.* in AJ volunteers without a diagnosis of breast or ovarian cancer.[21] This suggests that AJ founder mutations are not associated with an increased risk of DCIS in women who are not selected for early-onset disease or FH of breast or ovarian cancer, but the small sample size and lack of formal age-matching limits the ability to reach a definitive conclusion. In particular, very few women with early-onset DCIS were included in the unselected ascertainment, reflecting the usual age distribution of this disease.

In the clinic-based ascertainment of women with DCIS, in whom the mean age at diagnosis was lower, and a FH of OC and/or early onset breast cancer was common, *BRCA* mutations were identified in 12.7% of probands (11.9% of AJ and 13.5% of non-AJ women). This is consistent with the frequency of 13% in women with DCIS diagnosed before age 50 in a retrospective analysis of 10,000 consecutive patients referred for genetic testing, and slightly less than the 17% (222 of 1,281) prevalence of *BRCA* mutations observed among women with IBC before age 50 referred for genetic testing at our institution during this same period.[18] This comparison is limited by several factors. Pathology reports confirming invasive disease were not available for all of the women with IBC, and misclassification bias could affect the comparison. Also, during the interval covered by this study, AJ ethnicity was slightly less common in women undergoing testing for IBC at our institution (49%) than in the DCIS cases reported here (53%). AJ ethnicity was not associated with an increased prevalence of

mutations among the women with DCIS, but an IBC cohort with fewer AJ women would be expected to have a lower mutation prevalence than one with a greater proportion of Jewish women, narrowing the apparent differential between DCIS and IBC. A definitive comparison of frequencies of *BRCA* mutations in DCIS and IBC in clinic-based series would require matching for age at diagnosis, ethnicity, and pedigree structure, as well as limiting ascertainment to kindreds that have not previously been tested for *BRCA* mutations.

BRCA mutations may have been more prevalent in the clinic-based ascertainment because of increased breast cancer screening in women with family histories of breast or ovarian cancer. Adem *et al.* have suggested that all stages of carcinogenesis occur in *BRCA* mutation-associated breast cancer, but that the process occurs more quickly than in sporadic breast cancer.[22] This would lead to a shorter *in situ* phase and, possibly, to a lower likelihood of identifying *in situ* cancers with conventional screening techniques and intervals. Women referred for genetic risk assessment, many of whom have a FH consistent with the HBOCS, may participate in more frequent screening than women in the general population. This more frequent screening may identify *BRCA*-associated breast cancers in their relatively short *in situ* phase. In women without a family history that would prompt genetic risk assessment, undergoing less intensive breast cancer screening, *BRCA*-associated cancers may progress to invasion before detection. Alteratively, the DCIS lesions identified in the women in the clinical ascertainment may be incidental, and not related to the underlying genetic predisposition.

FH factors predictive of *BRCA* mutation status in DCIS probands referred for genetic risk assessment were identified in this study. Multivariate analysis revealed that FH of OC and early onset BC were strongly predictive of mutation status (OR 13.35, and 16.23, respectively). These risk factors are similar to those previously reported both for IBC and DCIS, and are also associated with mutation detection in unaffected women. Frank *et al.* identified FH of OC and early onset breast cancer as risk factors for *BRCA* mutations among probands with IBC and DCIS, as have many other investigators.[18] Claus *et al.* found that DCIS cases with *BRCA* mutations were more likely to have personal histories of OC and FH of early onset breast cancer.[17]

The present study has certain limitations. For the nested case-control studies, prevalent and incident ascertainments were combined to improve power. As survival from DCIS approaches 100%, there is no obvious reason to suspect significant differences in mutation prevalence between incident and prevalent cohorts, but larger sample sizes would be required to exclude such an effect. Family history information was not available for the unselected groups, which also limits the conclusions that

can be drawn. In the clinical ascertainment, some of the AJ probands only underwent testing for AJ founder mutations while others also underwent full sequencing. It is possible that some non-founder mutations were missed in the probands for whom full sequencing was not performed, however the number of such mutations is unlikely to be high enough to affect the conclusions. Finally, self-report was used to determine FH, a practice which may be subject to error.

This study indicates that women presenting for hereditary risk assessment with a personal history of DCIS may be found to carry *BRCA* mutations, particularly if they have significant family histories of ovarian cancer or early-onset breast cancer. The findings support, but do not prove, the presence of an *in situ* phase of carcinogenesis in the development of at least some *BRCA*-associated breast cancers. This emphasizes the potential benefit of screening in mutation carriers, which may identify cancers while in an *in situ* phase. The comparatively lower prevalence of mutations in women with DCIS compared to those with invasive cancer suggests that a pre-invasive phase, if it exists, may be shortened in a significant proportion of *BRCA*-associated breast cancers. Clinical trials to evaluate the benefit of screening at more frequent (e.g. semi-annual) intervals may address this possibility.

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